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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/285,531	04/02/1999	YUTI CHERNAJOVSKY	KIR95-01A	3818

7590 05/30/2003

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EXAMINER	
O HARA, EILEEN B	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 05/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/285,531	CHERNAJOVSKY ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,8,14-17 and 19-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,8,14-17 and 19-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 19, 2003 has been entered.

Status of Claims

2. Claims 1-3, 6, 8, 14-17, 19-37 are pending in the instant application. Claims 20-23, 27 and 34-37 have been amended as requested by Applicant in Paper Number 25, filed March 19, 2003.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3.1 The rejection of claims 1-3, 6, 8, 14-17 and 19-37 are maintained under 35 U.S.C. 103(a) as being unpatentable over Wallach et al., U.S. Patent No. 5,478,925, for reasons of record in the previous Office Actions, Paper No. 2, Paper No. 20 at pages 2-5, Paper No. 18, at pages 4-7, and Paper No. 8, at pages 2-3, and reiterated below.

Wallach describes and claims multimers of TNFR moieties, each such moiety corresponding to a soluble TNFR polypeptide (abstract), *e.g.*, the extracellular domains of the p55 and p75 human TNFRs (see column 1). It teaches that because both TNF and its receptors function *in vivo* as trimers, the multimeric receptors will be more effective than monomeric soluble receptors in binding to and inhibiting TNF (column 3, lines 10-38). It teaches that dimers or trimers of the TNFR moieties may be advantageously made (claims 2, 3). It teaches that the monomers should be separated by linker moieties of "optimum length... to produce multimers which best bind TNF" and that "[t]hose of ordinary skill in the art will be able to determine" such optimum length. It notes that "the nature of the amino acids which link the monomers in the recombinantly produced multimer is not critical." Wallach also teaches that the multimers may be conveniently made as contiguous fusion proteins by recombinant methods (column 4, lines 14-34 and Example 4), incorporating signal sequences as appropriate to the host cell system employed (paragraph bridging columns 12-13). It teaches that the multimers are suitable for the treatment of various TNF-mediated diseases and disorders, including septic shock, cachexia, GVHD, and various autoimmune diseases including rheumatoid arthritis (column 4, lines 42-55). Wallach does not exemplify the preparation of any particular fusion multimer, nor does it specify the amino acid sequences of the TNFR monomers or the linker peptides.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a fusion protein comprising two or three human p55 and/or p75 TNFR extracellular domain sequences, joined by suitable linker sequences and optionally comprising a signal sequence for production in an appropriate host cell, because Wallach teaches

that it is advantageous to do so. In the course of making such fusions, it would have been obvious to construct DNA encoding the fusion polypeptide by excising the TNFR sequences from vectors available in the art, ligating them, and transforming suitable host cells, and to obtain the fusions by expression in the transformed host cells, because Wallach teaches that the fusions it describes are conveniently made by such methods. Finally, it would have been obvious to use the fusion proteins thus produced to inhibit TNF, as in the treatment of diseases including particularly rheumatoid arthritis, because Wallach teaches that the multimers are advantageously employed for such purposes. The claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

3.2 The rejection of claims 1-3, 6, 8, 14-17 and 19-37 are maintained under 35 U.S.C. 103(a) as being unpatentable over Wallach et al., EP 0 526 905, for reasons of record in the previous Office Actions, Paper No. 2, Paper No. 20 at pages 2-5, Paper No. 18, at pages 4-7, and Paper No. 8, at pages 3-4, and reiterated below.

The Wallach EP publication is substantially identical to the U.S. patent relied upon in the rejection above. Wallach '905 describes and claims multimers of TNFR moieties, each such moiety corresponding to a soluble TNFR polypeptide, including particularly the extracellular domains of the p55 and p75 human TNFRs (abstract; page 2). It teaches that because both TNF and its receptors function *in vivo* as trimers, the multimeric receptors will be more effective than monomeric soluble receptors in binding to and inhibiting TNF (page 3, lines 3-19). It teaches that the monomers should be separated by linker moieties of different lengths and that "the optimal linker length will be defined" by routine experimentation (page 7, lines 18-21). It teaches that either peptide or non-peptide linkers, and it teaches that the multimers may be

conveniently made as contiguous fusion proteins by recombinant methods (Example 4, pages 7-9), incorporating signal sequences as appropriate to the host cell system employed (page 9, lines 22-28). It teaches that the multimers are suitable for the treatment of various TNF-mediated diseases and disorders, including septic shock, cachexia, GVHD, and various autoimmune diseases including rheumatoid arthritis (page 3, lines 29-33). The '905 publication does not exemplify the preparation of any particular fusion multimer, nor does it specify the amino acid sequences of the TNFR monomers or the linker peptides.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a fusion protein comprising two or three human p55 and/or p75 TNFR extracellular domain sequences, joined by suitable linker sequences and optionally comprising a signal sequence for production in an appropriate host cell, because Wallach teaches that it is advantageous to do so. In the course of making such fusions, it would have been obvious to construct DNA encoding the fusion polypeptide by excising the TNFR sequences from vectors available in the art, ligating them, and transforming suitable host cells, and to obtain the fusions by expression in the transformed host cells, because Wallach teaches that the fusions it describes are conveniently made by such methods. Finally, it would have been obvious to use the fusion proteins thus produced to inhibit TNF, as in the treatment of diseases including particularly rheumatoid arthritis, because Wallach teaches that the multimers are advantageously employed for such purposes. The claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

3.3 The rejection of claims 1-3, 6, 8, 14-17 and 19-37 are maintained under 35 U.S.C. 103(a) as being unpatentable over Smith et al. PN 5,395,760, March 7, 1995, for reasons of record in the

previous Office Actions, Paper No. 2, Paper No. 20 at page 5, Paper No. 18, at page 7, and reiterated below.

Claims 1-3, 6, 8, 14-17 and 19-37 encompass receptor molecules which bind to tumor necrosis factor comprising all or a functionally portion of two or three extracellular domains of tumor necrosis factor receptors linked via polypeptide linker(s), nucleic acids encoding them, and methods of treatment.

Smith et al. disclose a p75 TNFR (Fig. 2A), and teach at column 10, lines 33-39:

"Both monovalent forms and polyvalent forms of TNF-R are useful in the compositions and methods of the invention. Polyvalent forms possess multiple TNF-R binding sites for TNF ligand. For example, a bivalent soluble TNF-R may consist of two tandem repeats of amino acids 1-235 of Fig. 2A, separated by a linker region."

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to make a dimeric or polyvalent TNF receptor molecule comprising the extracellular domains of TNF-R, as suggested by Smith et al. One of ordinary skill in the art would have been motivated to do so, because of the number of different diseases found to be associated with TNF, and there would have been a reasonable expectation of success, since production of chimeric proteins was routine in the art at the time of the invention, and since TNF-R Ig fusions proteins were known to be effective for treatment.

Conclusion

4. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

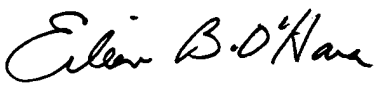
Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.



Patent Examiner